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Original Article

Hepatitis B reactivation: A possible cause of coronavirus disease 2019 vaccine induced hepatitis

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KEYWORDS
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Background and aims: Coronavirus disease 2019 (COVID-19) vaccines were rapidly implemented globally and vaccine-associated immune-related hepatitis was recently reported. We aim to investigate its impact in regions endemic of chronic hepatitis B (CHB).
Methods: We retrospectively collected patients who developed hepatitis within 90 days after COVID-19 vaccination in Taiwan. The mechanisms of hepatitis included vaccine induced liver injury (VILI) and immune-related hepatitis, which are direct liver injuries defined as aspartate or alanine aminotransferase (AST or ALT) increased $\geq$ 5-fold upper limit of normal (ULN) and/or AST or ALT $\geq$ 3-fold of ULN with concurrent total bilirubin $\geq$ 2-fold of ULN. Indirect liver injury due to HBV reactivation was defined as HBsAg reverse seroconversion or significant rise in HBV DNA level. The demographics, clinical data, and course of hepatitis were compared statistically.
Results: Twenty-five patients were included with a median age of 54. The culprit vaccines were ChAdOx1 nCoV-19 (n = 9), mRNA-1273 (n = 12), and BNT162b2 (n = 4). The characteristics of hepatitis were comparable regardless of vaccine subtypes. The median onset of hepatitis was 25 days post vaccination, with a peak of 10-fold ALT-increase. The etiologies

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included HBV reactivation (n = 10), VILI (n = 10), and immune-related hepatitis (n = 5). HBV reactivation accounts for 90% of vaccine-induced hepatitis in patients of CHB (n = 10), and two patients died. Patients with initial AST levels >500 U/L increased 27-fold risks of liver injury greater than moderate severity compared with those without.
Conclusions: COVID-19 vaccine induced hepatitis is a clinical significant complication, and HBV reactivation may account for a possible mechanism.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and the resulting coronavirus disease 2019 (COVID-19) overwhelmed the world at an unprecedented speed. As of early-January 2023, there were more than 656 million confirmed COVID-19 cases worldwide.[1] Vaccination against SARS-CoV-2 reduces disease severity, hospitalization and death. The pharmaceutical industries facilitated vaccine development. Vaccines were classified into four main categories, including the lipid-nanoparticle encapsulated mRNA,[2,3] adenovirus vector,[4] protein subunits,[5] and inactivated virus.[6] Several vaccines were validated with emergency use authorization and more than 12 billion doses had been administered globally.[1]

The COVID-19 vaccines advanced in mRNA-based technology and escalated the use of adenoviral vector-based vaccines. Long-term safety monitoring remained challenging. Frequent side effects in the trials were local injection—site reactions, myalgia, arthralgia, and fever.[2–6] Serious adverse events such as vaccine induced thrombotic thrombocytopenia[7] and myocarditis[8] were reported afterwards. Even later, Bril et al. reported on a case of autoimmune hepatitis after receiving COVID-19 vaccines.[9] Subsequently, several other case reports leading to a section of the European Association for the Study of the Liver position paper dedicated to hepatitis development after vaccination.[10–26] The speculated pathogenesis included a direct vaccine-related drug induced liver injuries (VILI),[14] autoimmune hepatitis,[9–11,13,15–24] and reactivation of hepatitis C.[12] The clinical course and outcomes of vaccine-related hepatitis remains unclear. Among areas with high prevalence of chronic hepatitis B (CHB), the potential liver toxicities warrant investigation. This study aims to study the characteristics and clinical course of vaccine induced hepatitis in Taiwan.

Materials and methods

The nationwide COVID-19 vaccination program started in Taiwan since March 2021. Four COVID-19 vaccines were administered, including the ChAdOx1 nCoV-19 (Azetra Zeneca, 26%), mRNA-1273 (Moderna, 38%), BNT162b2 (Pfizer, 31%), and MVC-COV1901 (Medigen, 5%).[27] Patients with abnormal liver function tests referred to the hepatology service of the National Taiwan University Hospital after COVID-19 vaccination were screened. We included patients who developed post-vaccination hepatitis and recorded their demographics and underlying liver diseases. Fatty liver was defined by increased echogenicity of liver by abdominal ultrasound. Types of vaccination, relevant laboratory data, liver pathology, treatment courses and outcomes were recorded for analyses. These patients were followed until liver aminotransferase recovery or until May 2022.

This study was approved by the Institutional Review Board of National Taiwan University Hospital (202202016RINB) and conformed to the ethical principles for medical research involving human subjects of the Declaration of Helsinki updated in 2013. The informed consents were waived because it was a retrospective review of medical records.

Ascertainment for etiology of vaccine induced hepatitis

There were direct and indirect mechanisms of vaccine induced hepatitis. Direct vaccination induced hepatitis was defined as aspartate or alanine aminotransferase (AST or ALT) increased ≥ 5-fold of upper limit of normal (ULN) and/or AST or ALT ≥ 3-fold of ULN with concurrent total bilirubin (T-bil) ≥ 2-fold of ULN.[25,28] Direct mechanisms included "vaccine induced liver injury" (VILI) and "immune-related hepatitis". The former was diagnosed clinically, after exclusion of other etiologies, chronologically compatible, and in cases being re-challenged of the culprit vaccine, with deterioration of liver function again. The latter was based on the revised original scoring system of the international autoimmune hepatitis group,[29] and no further deterioration of liver function if being rechallenged. The tests in the scoring system included: alkaline phosphatase: AST (or ALT) ratio, immunoglobulin G level, auto-antibodies (anti-nuclear antibody, anti-smooth muscle antibody, anti-mitochondrial antibody, anti-liver kidney microsomal antibody, anti-liver cytosol antibody type 1), and viral hepatitis markers. The other factors involved are as followed: sex, histological features and responsiveness to steroid if feasible. "HBV reactivation" was an indirect effect of vaccines, and was defined as HBsAg reverse seroconversion from HBsAg negative patients or a significant HBV DNA elevation, ≥10-fold of baseline, ≥1000 IU/mL (baseline undetectable), or ≥10000 IU/mL (no available baseline) for HBsAg positive patients. Hepatitis B flare was defined as HBV reactivation and ALT elevation ≥ 3-fold of ULN.

Patients met the above criteria within 90 days post-vaccination were included. The severity of liver injury was stratified as mild, if T-bil $<$ 2-fold of ULN; moderate, if T-bil $\geq$ 2-fold of ULN; severe, if T-bil $\geq$ 2-fold of ULN and international normalized ratio $\geq$1.5, ascites, or encephalopathy; or fatal, if death.[28]

Statistical analysis

Continuous variables were presented as the median (range) and categorical data as the number (percentage). Differences between the groups were evaluated using Mann–Whitney U test, chi-square test or Fisher's exact test as appropriate. Wilcoxon signed-rank test was used to compare the baseline and peak HBV DNA levels. Clinically relevant and significant variables associated with hepatitis in univariate analysis were included in multivariable logistic regression analysis, and odds ratios (ORs) and 95% confidence intervals were calculated. All statistical analyses were performed using STATA (version 16; Stata Corp, College Station, TX). All tests were two sided, and a P value of $<$0.05 was considered statistically significant.

Results

Between March 2021 and March 2022, a total of 25 cases were included. There were 16 men (64%) with median age of 54 (range: 21–81) and median BMI of 22.1 (range: 17.3–31.0). Among them, 18 had underlying liver diseases (10 chronic hepatitis B [40%], 4 fatty liver [16%], 1 resolved hepatitis B [4%], 1 hepatitis C reached sustained virological response after treatment [4%], 1 triptorelin related drug induced liver injury [4%], and 1 autoimmune hepatitis with primary biliary cholangitis [AIH-PBC, 4%]). The most common culprit vaccine was mRNA-1273 (n = 12, 48%), followed by ChAdOx1 nCoV-19 (n = 9, 36%) and BNT162b2 (n = 4, 16%) (Supplementary Table 1). The median latency between vaccination to hepatitis was 25 days (range: 2–80) with a median peak ALT level of 401 U/L (range: 51–5516). Forty-eight percent of patients (n = 12) had clinical symptoms for hepatitis (nausea, malaise, jaundice, and abdominal fullness). For other patients, liver dysfunction was found incidentally at their regular laboratory examinations for their underlying diseases or health checkup. The median duration for ALT recovery was 73 days (range 7–188, n = 21), while 4 still had abnormal ALT level until the end-of-follow-up. The etiologies of hepatitis were HBV reactivation (n = 10, 40%), VILI (n = 10, 40%), and immune-related hepatitis (n = 5, 20%). The severity of the liver injury was categorized as mild (n = 18, 72%), moderate (n = 5, 20%), and fatal (n = 2, 8%).

Post-vaccination hepatitis by etiologies

CHB reactivation

There were 10 HBV reactivation patients without cirrhosis at baseline (Table 1). Only 4 patients presented with associated symptoms initially. The median age was 55 and 70% were men. Their median ALT level at hepatitis was 178 U/L, and there was a significant increase in HBV DNA level from their baseline (7.21 vs. 3.66 $\log_{10}$ IU/mL, P = 0.016). None of the patients were under nucleos(t)ide analogue (NA) therapy at hepatitis onset and six (60%) patients started to receive NA therapy after hepatitis occurred. In one patient (Case 1) who developed HBV flare after 1st dose of mRNA-1273 vaccine, the NA therapy prevented further liver dysfunction even after the 2nd dose. However, HBV reactivation after vaccination could be fatal. Eight patients (80%) of CHB developed HBV-flare after mRNA-1273 (n = 6) or ChAdOx1 nCoV-19 (n = 2) vaccine. Two were hospitalized and unfortunately deceased despite of prompt NA therapies and intensive medical treatment.

Case 5 was a 57-year-old man previously treated with entecavir for more than 2 years with undetectable HBV DNA and normal ALT level at end of treatment. After discontinuing entecavir, he remained sustained virological remission (HBV DNA $<$2000 IU/mL) with normal ALT level for 16 months. He had HBV DNA level 760 IU/mL before COVID-19 vaccination. After he received 2 doses of mRNA-1273 vaccination, hepatitis developed (peak ALT: 1040 U/L, peak HBV DNA 948,000,000 IU/mL) 20 days later, and he received tenofovir alafenamide promptly. However, liver function deteriorated, and during liver transplantation evaluation, he was found to be HIV-positive with a CD4 count as low as 125 cells/μL. Bictaegravir and emtricitabine were applied additionally; nevertheless, he died of hepatic failure and uncontrolled sepsis 9 days after admission.

Case 7 was a 38-year-old and 20-week pregnant lady under prednisolone 10 mg/day for 3 months for her autoimmune thyroiditis. She was a known HBV carrier but lost to follow up in the past 2 years. Her last ALT record was 14 U/L but no baseline HBV DNA was tracible. She presented with icteric sclera and yellowish discoloration of the skin 5 days after the 1st dose of mRNA-1273 vaccination. Hepatitis B flare was detected (ALT 1745 U/L, T-bil 4.1 mg/dL, INR 1.74, HBV viral load $>$1,000,000,000 IU/mL) and tenofovir disoproxil fumarate was prescribed. Nonetheless, progressive hepatic decompensation, vaginal bleeding, profound hypotension and lactic acidosis developed. She was admitted to the intensive care unit, and plasma exchange and continuous venovenous hemodiafiltration were started. Vaccine related catastrophic anti-phospholipid syndrome with multi-organ failure was suspected by a rheumatologist. Belimumab, cyclosporin, abatacept, leflunomide and methylprednisolone were administered. Unfortunately, the patient passed away on day 26 (Fig. 1).

Case 4 was an 81-years old man with resolved hepatitis B (HBsAg negative, anti-HBc positive, anti-HBs antibody positive). He received 2 doses of mRNA-1273 vaccines and hepatitis developed (T-bil 1.03 mg/dL and ALT 103 U/L) 35 days later. The HBsAg was reversely sero-converted to be positive, with negative anti-HBs and IgM anti-HBc. The HBV DNA level was 6,100,000 IU/mL. He was closely monitored without treatment. The ALT reduced to 64 U/L at day 74 but the patient lost to follow-up afterwards.

Vaccine related drug induced liver injury (VILI)

There were 10 presumed VILI victims (Table 2). Three patients developed hepatitis after their 1st dose and 7 after the 2nd dose of vaccination. The median age was 41 and 60% were men. At hepatitis onset, the median ALT was 161 U/L. They were excluded for autoimmune hepatitis (AIH) and other viral hepatitis. The clinical course of VILI was

Table 1 Patient characteristics of HBV reactivation after COVID-19 vaccination.

Case No.	Age/sex/ underlying liver disease	Culprit vaccine	Latency (days)[a]	Onset/peak AST (U/L)	Onset/peak ALT (U/L)	Baseline/ peak HBV DNA (IU/mL)	Treatment	Recovery (days)[b]	Severity
1	53/M/CHB	mRNA-1273	74	259/259	587/587	2510/1,440,000	LdT	37	Mild
2	55/M/CHB	ChAdOx1	4	688/688	1956/1956	NA/64,700	ETV	47	Moderate
3	37/M/CHB	ChAdOx1	33	86/167	235/401	97600/5,110,000	NA	109	Mild
4	81/M/Resolved B	mRNA-1273	35	91/91	103/103	NA/6,100,000	NA	NA	Mild
5	57/M/CHB	mRNA-1273	20	65/1113	63/1040	760/948,000,000	TAF	NA	Fatal[c]
6	47/M/CHB	mRNA-1273	39	468/468	791/791	9430/165,000	NA	34	Mild
7	38/F/CHB	mRNA-1273	8	1387/1387	1745/1860	NA/>1,000,000,000	TDF	11	Fatal
8	55/M/CHB	mRNA-1273	27	60/1340	121/2212	<20/125,000,000	TAF	188	Moderate
9	62/F/CHB	mRNA-1273	11	45/45	59/59	4520/16,100,000	NA	73	Mild
10	66/F/CHB	mRNA-1273	23	59/241	97/245	99600/343,000,000	TAF	172	Mild

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHB, chronic hepatitis B; ETV, entecavir; LdT, telbivudine; NA: Not available or not applicable.
Resolved B, resolved hepatitis B infection; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.
[a] Between the onset of hepatitis and the culprit vaccination.
[b] AST or ALT normalized to baseline value or upper limit of normal.
[c] HIV-coinfection.

relatively benign. Eight patients (80%) recovered spontaneously while 2 (20%) patients were treated with a short course prednisolone (0.3—0.5 mg/kg/d). Only one patient (10%) developed moderate liver injury and was hospitalized. There was no mortality.

Case 14 was a 43-year-old woman with underlying fatty liver disease. She received ChAdOx1 nCoV-19 vaccine as first dose and experienced worsening malaise and visited a local clinic 2 days later, where ALT rose to 5516 U/L. She visited our clinic 12 days later with resolved symptoms, improving ALT and viral hepatitis was excluded. ALT normalized in 26 days.

Case 17 was a 30-year-old man and his ALT increased to 153 U/L 78 days after the ChAdOx1 nCoV-19 vaccine. He went on to inoculate mRNA-1273 vaccine, and his ALT increased to 212 U/L one week later. His ALT recovered 109 days after hepatitis onset.

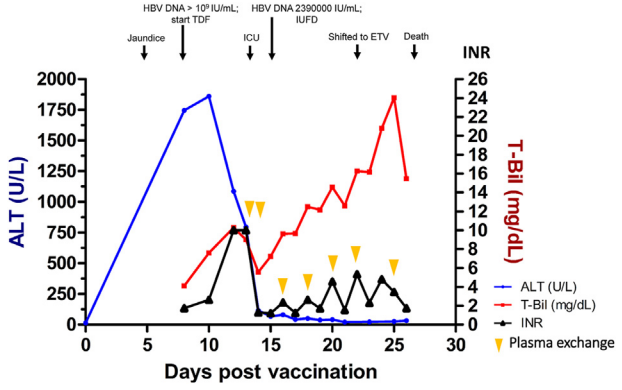

Figure 1 Clinical course of case 7 with chronic hepatitis B reactivation after COVID-19 vaccine. ICU, intensive care unit; IUFD, intra-uterine fetal demise; TDF, tenofovir; ETV, entecavir; Baseline ALT 14 U/L was recorded as the ALT value on day 0; INR level were >10 on day 12 and 13 and to illustrate, we used the value of 10 on the figure.

Immune-related hepatitis

Among the 5 presumed immune-mediated hepatitis patients, the median age was 64, and 60% were men (Table 3). Three had positive anti-nuclear antibody (1:80 to > 1:2560) and 1 had high anti-smooth muscle antibody (1:80). One patient had concurrent anti-mitochondrial antibody (>1:320). The median immunoglobulin G level was 1585 mg/dL (n = 4). The pre-treatment AIH score was 10 for 1 patient and 12 for 2 patients. Post-treatment AIH score were 14 for another patient, which all fulfilled the criteria of probable AIH. Four patients (80%) developed hepatitis after the first dose of vaccination, while two received the second dose as re-challenge. There was no further deterioration in liver function. These patients were also excluded for other causes of hepatitis, such as viral, drug-induced, or steatohepatitis.

Two patients developed moderate liver injury; one fully recovered while one was improving spontaneously. The other two received treatment with prednisolone (0.5 mg/kg/day) and ursodiol (12 mg/kg/day) respectively. Only one patient was hospitalized whereas no mortalities were observed.

Liver pathology of post-vaccination hepatitis

Five patients received liver biopsies to clarify the cause of hepatitis. All of them had active hepatitis which included lobular lymphocytic infiltration, hepatic rosette formation, lobular disarray, and necroinflammatory activities. (Case 21 [Immune-related hepatitis], Fig. 2A) The severity varied from mild to moderate necroinflammatory activity (n = 4) to bridging necrosis (n = 1, case 21, Fig. 2B). There were also portal inflammation and interface hepatitis (Case 21, Fig. 2C). Case 11 with VILI demonstrated prominent sinusoidal histiocytic infiltrate with microgranuloma formation (Fig. 2D). Of note, a cirrhotic background was present on case 23 with immune-related hepatitis (Fig. 2E). Along with her laboratory result, we presumed that the patient had suffered from AIH-PBC overlap syndrome and vaccination unmasked the underlying disease.

Table 2 Patient characteristics of vaccine induced liver injury after COVID-19 vaccination.

Case No.	Age/sex/ underlying liver disease	Culprit vaccine	Latency (days)[a]	Onset/peak AST (U/L)	Onset/peak ALT (U/L)	Auto-antibodies	Treatment	Recovery (days)[b]	Severity
11	39/F/NA	ChAdOx1	27	2176/3056	2217/2568	ANA 1:80 (−), ASMA 1:40 (−), anti-LKM 1:10 (−), AMA 1:40 (−)	NA	61	Moderate
12[c]	70/M/NA	ChAdOx1	7	39/172	101/140	ANA 1:1280 (+), ASMA 1:40 (−), AMA 1:40 (−)	PDN 0.5 mg/kg/d	66	Mild
13	54/M/Fatty liver	ChAdOx1	44	565/565	1293/1293	ANA 1:80 (−), ASMA 1:40 (−), anti-LKM 1:10 (−), anti-LC1 1:10 (−), AMA 1:40 (−)	PDN 0.3 mg/kg/d	92	Mild
14	43/F/Fatty liver	ChAdOx1	2	700/700	5516/5516	NA	NA	26	Mild
15	27/M/Fatty liver	mRNA-1273	8	268/268	748/748	ANA 1:40 (−), ASMA 1:40 (−), anti-LKM 1:10 (−), AMA 1:10 (−)	NA	NA	Mild
16[d]	71/F/CHB	BNT162b2	16	83/161	168/344	NA	NA	81	Mild
17	30/M/Fatty liver	ChAdOx1	78	63/122	153/212	ANA 1:80 (−), ASMA 1:40 (−), anti-LKM 1:10 (−), AMA 1:40 (−)	NA	109	Mild
18	37/M/NA	BNT162b2	21	224/224	51/51	ANA 1:40 (−), AMA 1:10 (−)	NA	7	Mild
19	55/F/HCV SVR	BNT162b2	25	374/374	121/121	ANA 1:80 (−), ASMA 1:40 (−), anti-LKM 1:10 (−), AMA 1:40 (−)	NA	58	Mild
20	33/M/NA	ChAdOx1	61	376/376	106/106	ANA 1:80 (−), ASMA 1:40 (−), anti-LKM 1:10 (−), AMA 1:40 (−)	NA	83	Mild

ALT, alanine aminotransferase; AMA, anti-mitochondrial antibody; ANA, anti-nuclear antibody; Anti-LC1, anti-liver cytosol antibody type 1; Anti-LKM, anti-liver kidney microsomal antibody; ASMA, anti-smooth muscle antibody; AST, aspartate aminotransferase; CHB, chronic hepatitis B; HCV SVR, hepatitis C with sustained virological response; NA: Not available or not applicable; PDN, prednisolone.

[a] Between the onset of hepatitis and the culprit vaccination.

[b] AST or ALT normalized to baseline value or upper limit of normal.

[c] Case 12 did not meet the diagnostic criteria of revised original scoring system of the international autoimmune hepatitis group despite high ANA titer. Clinically, the liver function continued to improve during the course of steroid tapering.

[d] Case 16's HBV DNA prior to vaccination was 11,200 IU/mL and 66,900 IU/mL at hepatitis onset.

Table 3 Patient characteristics of immune related hepatitis after COVID-19 vaccination.

Case No.	Age/sex/underlying liver disease	Culprit vaccine	Latency (days)[a]	Onset/ peak AST, U/L	Onset/peak ALT, U/L	Auto-antibodies	Diagnosis	Treatment	Recovery (days)[b]	Severity
21	64/M/NA	mRNA-1273	40	1071/1071	1147/1147	ANA 1:80 (−), ASMA 1:40 (−), Anti-LKM 1:10 (−), AMA 1:40 (−)	AIH score 14[c]	PDN 0.5 mg/kg/d	44	Moderate
22	68/M/DILI[d]	mRNA-1273	26	219/219	251/252	ANA >1:2560 (+), ASMA 1:40 (−), Anti-LKM 1:10 (−)	AIH score 12	NA	98	Mild
23	76/F/AIH-PBC	mRNA-1273	15	168/168	112/112	ANA 1:80 (+), ASMA 1:40 (−), Anti-LKM 1:10 (−), Anti-LC1 1:10 (−), AMA> 1:320 (+)	AIH-PBC	Ursodiol 12 mg/kg/d	91	Mild
24	21/M/NA	ChAdOx1	3	51/51	211/211	ANA 1:40 (−), ASMA 1:80 (+), Anti-LKM 1:10 (−)	AIH score 10	NA	158	Mild
25	51/F/NA	BNT162b2	80	542/542	914/914	ANA 1:160 (+), Anti-LKM 1:10 (−), AMA 1:40 (−)	AIH score 12	NA	NA	Moderate

ALT, alanine aminotransferase; AIH, autoimmune hepatitis; AIH-PBC, autoimmune hepatitis and primary biliary cholangitis; AMA, anti-mitochondrial antibody; ANA, anti-nuclear antibody; Anti-LC1, anti-liver cytosol antibody type 1; Anti-LKM, anti-liver kidney microsomal antibody; ASMA, anti-smooth muscle antibody; AST, aspartate aminotransferase; DILI, drug-induced liver injury; NA: Not available or not applicable; PDN, prednisolone.

[a] Between the onset of hepatitis and the culprit vaccination.

[b] AST or ALT normalized to baseline value or upper limit of normal.

[c] If treatment was given, AIH score was calculated as post-treatment score.

[d] DILI induced by diphereline.

Post-vaccination hepatitis according to vaccine or CHB status

Regarding their vaccination, 9 received adenovirus-vector vaccines and 16 received mRNA vaccines (12 mRNA-1273 and 4 BNT162b2). The patients receiving adenovirus-vector based vaccine were younger (39 vs. 56 years old, $p = 0.039$). Other than that, the patterns of liver injury, causes of hepatitis, severities and prognoses were comparable (Supplementary Table 2).

We further investigate the hepatitis between CHB and non-CHB groups (Table 4). In 10 CHB patients, 2 (20%) progressed to moderate liver injury and 2 (20%) died of liver failure even after prompt NA therapy. On the other hand, 3 (20%) of 15 non-CHB patients developed moderate liver injury. Among these patients, 2 had fully recovered and one was improving. The etiologies of hepatitis were significantly different between CHB and non-CHB groups ($p < 0.001$). In CHB patients, 90% hepatitis was due to HBV reactivation, while in non-CHB patients, 60% were due to VILI, 33% because of immune-related hepatitis, and one developed HBV reactivation. There was no significant difference between the 2 groups regarding liver injury patterns, severities, hospitalization, and mortality.

Predictors for severe liver injury

Seven patients developed liver injuries $\geq$ moderate severity. Univariate analysis showed that greater initial AST level significantly increased the risks of more severe liver injury. Using AST level to predict $\geq$ moderate severity post vaccination had an area under the receiver operating characteristic curve of 0.76. A cut-off 500 U/L of AST was selected by the Youden index. Multivariable logistic regression analysis after adjusting age and sex demonstrated that patients with AST >500 U/L possess 27-fold higher risks of liver injury $\geq$ moderate severity comparing with those with lower AST level. (Adjusted OR: 26.97, 95% CI: 2.13—342, $p = 0.011$) (Table 5).

Discussion

In our series, we demonstrated that the causes for hepatitis after vaccination included HBV reactivation, VILI and immune-related hepatitis. Moreover, the etiologies appeared distinct in patients with and without CHB. On the contrary, types of vaccines did not make differences.

Since the global COVID-19 vaccination, several case reports demonstrated hepatitis after the vaccine.[9—24] The largest series to date, included 87 patients across 18 countries was presented by Efe et al.[25] The clinical characteristics from the series were female predominant (63%), with a median age of 48. The median duration between vaccination to hepatitis onset was 15 days with 92% of them being symptomatic at presentation. The liver injury was hepatocellular pattern predominance (84%).

However, many Asian countries are endemic for CHB with a large population of significant liver diseases. The adverse impact of COVID-19 vaccines in liver of these regions might increase. In our series, reactivation of CHB constitutes the major cause (40%) for post-vaccination hepatitis. On the contrary, 52% of the patients who were diagnosed as immune-related hepatitis in the above case series. Despite of

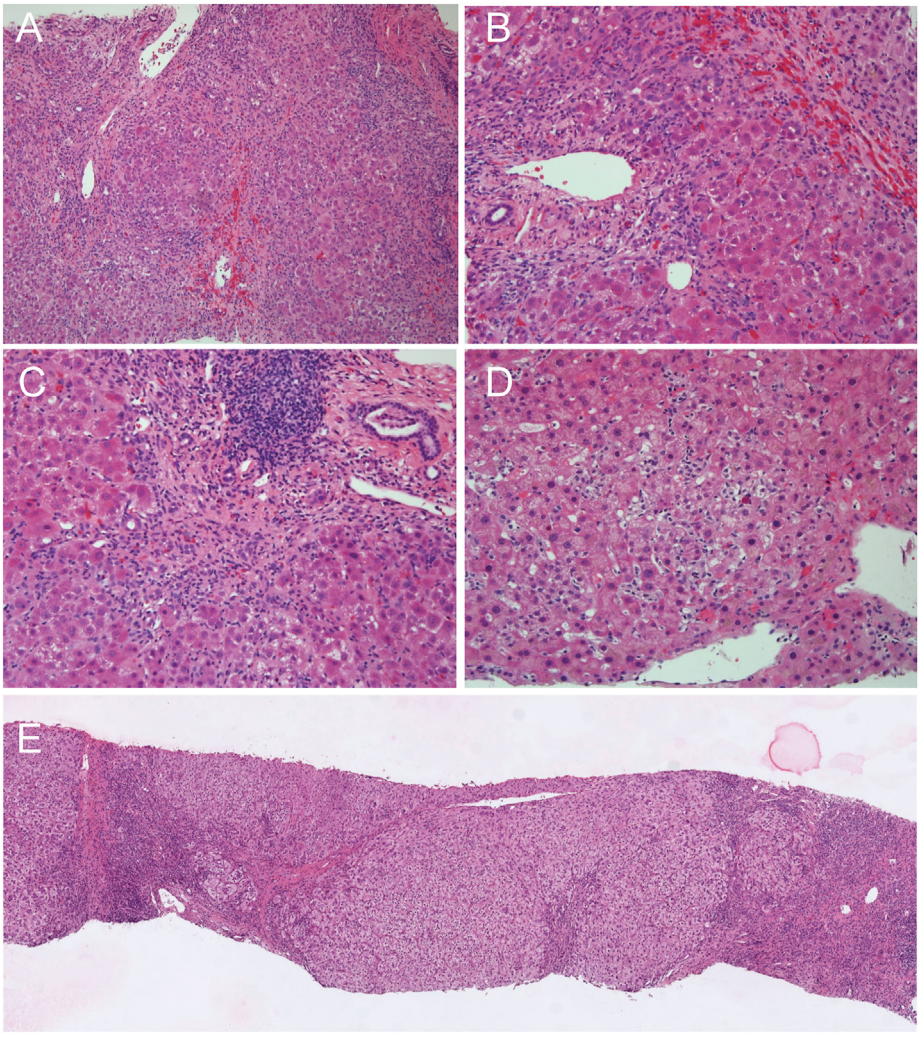

Figure 2 The pathological findings of vaccination induced hepatitis. (A) Lobular lymphocytic infiltration, hepatic rosette formation, lobular disarray, and necroinflammatory activities. H&E stain, 100X (B) bridging necrosis. H&E stain, 200X (C) portal inflammation and interface hepatitis. H&E stain, 200X. (D) Prominent sinusoidal histiocytic infiltrate with microgranuloma formation. H&E stain, 200X. (E) A cirrhotic background in a patient with autoimmune hepatitis and primary biliary cholangitis. H&E stain, 40X.

different mechanisms, the general prognoses were favorable. Nonetheless, 2 mortalities were observed due to CHB flare in our series and a patient underwent liver transplantation due to AIH-like hepatitis in the above series.

The major finding of this study is that COVID-19 vaccination may reactivate hepatitis B. There was one report on HBV reactivation triggered by COVID-19 infection.[30] However, our patients were unlikely COVID-19 victims due to the low prevalence COVID-19 in Taiwan during the study period, and all hospitalized patients were tested COVID-19 negative. The increasing HBV DNA level confirmed their HBV reactivation, and even one resolved hepatitis B patient seroconverted to HBsAg-positive. Although we cannot evaluate the true incidence of HBV reactivation, our series suggested that liver function tests and HBV viral load should be monitored after COVID-19 vaccination.

The type of drug induced liver injury from COVID-19 vaccination may be idiosyncratic. Case 17 received heterologous vaccination. The 1st dose, ChAdOx1 nCoV-19, uses replication-incompetent adenovirus to carry the spike protein gene. The 2nd dose, mRNA-1273 is the lipid-nanoparticle encapsulated purified mRNA that codes for the spike protein. Although stemming from different mechanisms, both vaccines lead to the production of SARS-CoV-2 spike proteins. Because SARS-CoV2 may have direct hepatotoxicity[31]; thus, in this case, we speculated that the spike protein may cause liver injury but required confirmation.

Earlier case reports had demonstrated portal vein thrombosis related abnormal liver function after COVID-19 vaccination.[7] Among our biopsied patients, no vascular alteration was observed. Instead, AIH-like pathological features could be noted after either vaccination. In accordance to a recent international cohort study, lobular hepatitis and presences of autoantibodies were frequently observed.[32] There have been case reports on hepatitis after influenza and hepatitis A vaccination.[33,34] The etiology was speculated to be molecular mimicry resulting in AIH. Hypothesis from basic research had been proposed on mRNA

Table 4 Post-vaccination hepatitis according to HBV status.

Parameters	CHB (n = 10)	Non-CHB (n = 15)	P value
Age	55 (37–71)	51 (21–81)	0.488
Male	6 (60)	10 (67)	0.734
BMI	23.3 (20.3–31.0)	21.6 (17.3–27.9)	0.270
Onset of hepatitis			
Latency (days)[a]	22 (4–76)	26 (2–80)	0.618
T-bil (mg/dL)	0.9 (0.5–4.1)	1.1 (0.4–22.1)	0.215
AST (U/L)	85 (45–1387)	268 (39–2176)	0.318
ALT (U/L)	202 (59–1956)	211 (51–5516)	0.718
ALP (U/L)	83 (54–175)	74 (40–390)	0.511
γGT (U/L)	42 (20–166)	131 (12–378)	0.222
INR	1.1 (1.0–1.7)	1.0 (1.0–1.3)	0.405
Course			
Peak AST-increase (fold)[b]	11.7 (1.5–44.7)	8.6 (1.7–98.6)	0.618
Peak ALT-increase (fold)[b]	16.8 (1.4–54.0)	5.2 (1.2–134.5)	0.244
Recovery (days)[c]	73 (11–188) n = 9	75 (7–158) n = 12	0.972
Cause of hepatitis (%)			<0.001*
Immune related	0 (0)	5 (33)	
Vaccine induced liver injury	1 (10)	9 (60)	
Hepatitis B reactivation	9 (90)	1 (7)	
Prognosis (%)			
≥ moderate severity[d]	4 (40)	3 (20)	0.275
Hospitalization	2 (20)	2 (13)	>0.99
Mortality	2 (20)	0 (0)	0.150

Data are expressed as median (range) or number (percentage).
* Statistically significant, $P < 0.05$.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; γGT, gamma-glutamyl transferase; T-bil, total bilirubin.
[a] Between the onset of hepatitis and the culprit vaccination.
[b] Fold of peak AST or ALT elevation compared with upper limit of normal value.
[c] AST or ALT normalized to baseline value or upper limit of normal.
[d] Including moderate, severe, and fatal severity.

binding on pattern recognition receptors and subsequently activates pro-inflammatory cascades.[35] Our data demonstrated that SARS-CoV2 vaccine may induce immune responses and unmasked underlying autoimmune liver diseases. Nonetheless, the rare events of vaccine induced AIH led the European Medicines Agency's Pharmacovigilance Risk Assessment Committee to conclude that no causal relationships could be established.[36]

Table 5 Predictors for liver injury greater than moderate severity.

	Crude OR (95%CI)	P value	Adjusted OR (95%CI)	P value
Patient factors				
Age, 1 yr increase	1.00 (0.94–1.04)	0.581	1.01 (0.94–1.09)	0.738
Male	0.67 (0.11–3.99)	0.657	1.89 (0.15–23.25)	0.619
BMI, 1 kg/m^2 increase	0.97 (0.75–1.24)	0.788		
CHB	2.67 (0.45–15.96)	0.283		
AST, 1 U/L increase	1.00 (1.00–1.01)	0.039		
AST >500 U/L	20.00 (2.21–181)	0.008	26.97 (2.13–342)	0.011*
ALT, 1 U/L increase	1.00 (1.00–1.00)	0.313		
Vaccine factors				
Adenoviral-vector	1.00			
mRNA	1.59 (0.24–10.57)	0.631		
Cause of hepatitis				
Immune related	1.00			
Vaccine induced liver injury	0.17 (0.01–2.56)	0.199		
Hepatitis B reactivation	1.00 (0.11–8.95)	>0.99		

* Statistically significant, $P < 0.05$.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHB, chronic hepatitis B; CI, confidence interval; OR, odds ratio.

It is clinically important to identify the patients with more severe courses. We found patients with AST higher than 500 U/L, significantly increased risks of liver injury $\geq$ moderate severity. Current knowledge suggested the mechanism of liver injury from COVID-19 is mainly through activated systemic inflammatory response instead of direct cytotoxicity.[37] Therefore, AST, a rather non-hepatic specific marker has been established as a predictor for COVID-19 severity.[38] Since post-vaccination hepatitis was rare, there was no consensus on its definition. Although COVID-vaccine-related myocarditis was analyzed within 42 days after vaccination,[8] we prolong this limit because hepatitis could have an insidious onset without specific symptoms. Also, longer latent periods were required for HBV reactivation; therefore, hepatitis detection may be delayed. In addition, the latencies of idiosyncratic drug related hepatotoxicity are variable from days to months.[39]

A self-controlled case series based in Hong Kong suggested the risks of acute liver injury within 56 days post COVID-19 vaccination were not increased compared to the non-exposure periord.[40] However, the case numbers of post-vaccination hepatitis may be underestimated due to the unawareness of the possible hepatitis and HBV reactivation post vaccination. While more SARS-CoV-2 variants emerged, the vaccination policy evolved to heterologous vaccination with booster dosage, vaccine related adverse effects should be continuously monitored.

Due to the retrospective nature of our study and incomplete laboratory data or pathological information in some cases, determining the definite mechanism of liver injury may be challenging. As a result, we were unable to confirm whether the mechanisms were mutually exclusive and co-existence of multiple mechanisms was possible. In conclusion, post COVID-19 vaccination hepatitis is a rare yet severe complication that we need to be vigilant of, especially in CHB subjects. HBV reactivation should be closely monitored to implement antiviral NAs in time. It is our hope to bring awareness to the potential hepatitis risk meanwhile we acknowledge the importance of vaccination.

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Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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Abbreviations

AIH	autoimmune hepatitis
AIH-PBC	autoimmune hepatitis and primary biliary cholangitis
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CHB	chronic hepatitis B
COVID-19	coronavirus disease 2019
INR	international normalized ratio
NA	nucleos(t)ide analogue
OR	odds ratio
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
T-bil	total bilirubin
ULN	upper limit of normal
VILI	vaccine-related drug induced liver injuries

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jfma.2023.06.007.

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